PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2004/043950	29.12.2004	30.12.2003

International Patent Classification (IPC) or both national classification and IPC
C07D333/40, A61K31/381, A61P35/00, G01N33/68

Applicant
THE BRIGHAM AND WOMEN'S HOSPITAL, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/043950

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1, 2, 24-100 (industrial applicability), 101-106, 110-113

because:

☒ the said international application, or the said claims Nos. 24-100 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☒ the claims, or said claims Nos. 1, 2 are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1, 2, 101-106, 110-113

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3, 5-113
	No:	Claims	1, 2, 4
Inventive step (IS)	Yes:	Claims	3, 5-113
	No:	Claims	1, 2, 4
Industrial applicability (IA)	Yes:	Claims	1-23, 101-113
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III

Claims 24-100 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

The initial phase of the search for claims 1 and 2 revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, the search and the examination have been restricted to the compounds of present claim 3 and 4. The subject-matter of claims 101-106 and 110-113 has only been searched in view of the scope of the compound claims.

Re Item IV
Lack of unity of invention

Claims 101-106 and 110-113 are not limited to the scope of the claimed compounds. The claimed activity as such is, however, already known in the art, a single general inventive concept between the claimed compounds and the assay and the kit for the use in relation with other compounds than those of the present application is not detectable. This single inventive concept is defined as "involving one or more of the same or corresponding special technical features", which serve to distinguish the current application from the prior art (establishes novelty) and are responsible for the inventive activity. An objection concerning the unity of the invention must be expected in the regional phase.

Re Item V

1. PRIOR ART

Reference is made to the following documents:

D1: EP-A-0 234 622

D2: EP-A-1 176 139
D3: US 2003/187002 A1
D4: US 2002/042428 A1
D5: WO 99/55682 A
D6: WO 03/006047 A

2. NOVELTY

The subject-matter of claims 3, 5-113 is considered to be novel (Article 33(2) PCT). The essential structural difference between the claimed compounds and those of D1-D4 resides i.a. in the R2 substituent.

The subject-matter of claims 1 and 2 is at least anticipated by D1-D4 (Article 33(2) PCT), these documents represent only an arbitrary selection of the relevant prior art. D1-D4 disclose generic formula with overlapping definitions and examples falling within this overlap (cf. search report). According to page 58 (line 1-2) the compound of claim 4 was commercially available at the time of drawing up this application, therefore, novelty for this compound cannot be acknowledged.

3. INVENTIVE STEP

The subject-matter of claims 3-100 and 107-109 can be considered as involving an inventive step (Article 33(3) PCT). The document D5 is regarded as being the closest prior art to the subject-matter of these claims. It discloses HLA agonists and antagonists. The structures of the active compounds are, however, completely different from the presently claimed. The problem to be solved by the present invention is seen in the provision of further compounds with HLA activity. In view of the experimental part and the other information as given in the description, it can be assumed that this problem has been solved by the compound F15 (claim 4). The prior art D6 discloses further information which relates HLA-DM to HLA-DR. Due to the structural differences even the combined teaching of D5 and D6 would not motivate a man skilled in the art to arrive at the present invention.